II. REMARKS

Preliminary Remarks

Claims 1, 2, 4-10, 15, 17-20, 25, 49, 50, and 56 are amended, and claims 3, 16, and 44 are canceled by this response. Claims 1, 2, 4-15, 17-25, 42, 43, and 45-56 are pending following entry of the amendment.

Claims 1, 10, 15, 17, 18, 25, and 56 are amended to more clearly describe the claimed invention; *i.e.*, a method for the treatment or prevention of C-reactive protein (CRP)-mediated tissue damage comprising administering to a subject in need thereof an effective amount of a compound capable of inhibiting the binding of CRP to an autologous or extrinsic ligand thereof, *e.g.*, as described on page 3 (bottom paragraph).

Independent claims 1, 10, and 15 are further amended to specify that the inflammatory and/or tissue damaging condition that is treated or prevented by the claimed method is selected from an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia, as described on page 6, lines 18-22, and in original claim 3, which is canceled.

References in claims 1, 2, 10, 15, 49, and 50 to an "inflammatory and/or tissue-damaging condition" are deleted in view of the incorporation of the subject matter of claim 3 into claims independent claims 1, 10, and 15 as described above.

Claims 16 and 44, which are directed to a method for treating or preventing atherosclerosis, are canceled.

Claims 4-9, 19, and 20, are amended in their dependencies in accord with the cancellation of claims 3, 16, and 44.

Patentability Remarks

The following declarations by the inventor, Prof. Mark Pepys, are submitted herewith:

(i) a declaration pursuant to 37 C.F.R. § 1.132 providing experimental data,

(ii) a Katz declaration pursuant to 37 C.F.R. § 1.132, and

(iii) a declaration pursuant to 37 C.F.R. § 1.131 swearing behind a reference (Yeh et al.).

Prof. Pepys has reviewed and authorized the filing of the declarations; however, they are being submitted in unexecuted form because Prof. Pepys is currently traveling in foreign countries and cannot execute them at this time. The executed declarations will be submitted shortly under separate cover.

35 U.S.C. §112, first paragraph

Claim 1 is rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to enable one of skill in the art to treat atherosclerosis, but is not considered to provide enablement for preventing atherosclerosis or for treating or preventing tissue damage in general.

The applicant respectfully traverses the rejection of claim 1 under 35 U.S.C. §112, first paragraph, as being enabled only "for treating atherosclerosis." Independent claims 1, 10, and 15 have been amended to be directed to a method for the treatment or prevention of CRP-mediated tissue damage, and are further amended to specify that the tissue damage that is treated or prevented by the claimed invention is associated with a condition selected from the group consisting of an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia. Original claims 16 and 44, directed to a method for treating or preventing atherosclerosis, are canceled. The applicant submits that the specification fully enables one of skill in the art to practice the claimed method for treating or preventing CRP-mediated tissue damage successfully without having to perform undue experimentation, as discussed below. Furthermore, the applicant disagrees with the examiner's allegation that the application is enabled for a method for treating or preventing atherosclerosis *per se*.

Background

Atherosclerosis is a disease wherein the arterial inner wall thickens. If it becomes sufficiently severe it can reduce arterial blood supply to the heart, brain or periphery causing vascular insufficiency. An atherothrombotic event can occur as a complication of atherosclerosis in which an atherosclerotic plaque ruptures, triggering thrombotic occlusion of the effected artery and ischemic necrosis of the tissue supplied by that artery (*i.e.*, infarction – tissue damage resulting from obstruction of the blood supply). The tissue damage (ischemic necrosis) resulting from or associated with atherosclerosis is the cause of

death in about half of all individuals. The current best informed opinion is that CRP does not play a significant role in the pathogenesis of atherosclerosis. The observations set out in the present application and related academic papers by the Pepys group do not address prevention or treatment of either atherosclerosis or atherothrombosis. Again, please note that the original claims 16 and 44, which refer to treating or preventing atherosclerosis, are canceled.

Enablement

The amended claims of the present application are clearly directed to a method for the treatment or prevention of CRP-mediated tissue damage. As described in the application, and as specified in amended claims 1, 10, and 15, the tissue damage that is treated or prevented by the claimed invention is associated with a condition selected from the group consisting of an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia. As further specified in claims 2, 4-9, 17, 18, 49, 50, and 56, tissue damage that can be treated or prevented by the claimed invention includes tissue damage associated with any of the following conditions: atherosclerosis or a complication of atherosclerosis; a bacterial, viral, or parasitic infection; an allergic complication of rheumatic fever, glomerulonephritis, or erythema nodosum leprosum; an inflammatory disease selected from rheumatoid arthritis, juvenile chronic (rheumatoid) arthritis, ankylosing spondylitis, psoriatic arthritis, systemic vasculitis, polymyalgia rheumatica, Reiter's disease, Crohn's disease and familial mediterranean fever; tissue necrosis selected from myocardial infarction, tumor embolization and acute pancreatitis; trauma selected from elective surgery, burns, chemical injury, fractures and compression injury; malignant neoplasia selected from lymphoma, Hodgkin's disease, carcinoma and sarcoma; and stroke, whether it is a complication of atherosclerosis or has other causes. It must be kept in mind that the claimed method is for the treatment or prevention of CRP-mediated tissue damage that is associated with said condition.

The present application describes results obtained using an experimental *in vivo* model system in which tissue damage is caused by obstruction of blood supply and provides the first, and up to the present time the only, direct *in vivo* demonstration that CRP exacerbates tissue damage. The present application provides the first experimental evidence that CRP contributes to tissue damage *in vivo*, and that removal of CRP function from a

subject who has an inflammatory and/or tissue damaging condition involving elevated levels of CRP will treat or prevent tissue damage in that subject. Accordingly, the claims of the present application are directed to a method for treating or preventing such CRP-mediated tissue damage. The beneficial effects of the claimed invention are obtained for any inflammatory and/or tissue damaging condition involving elevated levels of CRP. The invention is therefore generally applicable. The application demonstrates that CRP contributes to tissue damage in general, as exemplified with reference to myocardial infarction in a rat model. Rats were treated to promote myocardial infarction. Infarct size was measured in the presence and absence of human CRP. Infarct size gives a direct measurement of the amount of tissue damage in the subject. The results are indicated in the section bridging pages 29 and 30 of the present application, and in Table 2. Table 2 provides data that shows that in animals receiving human CRP the mean infarct size is increased to be about 40% larger than in control animals that do not receive CRP. These results therefore demonstrate that the extent of tissue damage *in vivo* is directly affected by and increased in the presence of human CRP; *i.e.*, that human CRP directly exacerbates tissue damage *in vivo*.

Using a different experimental *in vivo* model system from that described in the present application, the inventor, Professor Mark Pepys, has demonstrated that human CRP contributes to tissue damage in the brain in the manner previously demonstrated for the heart. Gill et al. (J. Cerebral Blood Flow & Metabolism, 24(11):1214-1218, 2004), which is co-authored by Prof. Pepys, describes experimental results that show that damage to brain tissue (infarct size) resulting from obstruction of blood supply is significantly greater in rats receiving human CRP than in control rats that do not receive CRP. *See* page 3, second paragraph of Gill et al., a copy of which was submitted with the response filed on November 29, 2004. Gill et al. therefore presents further compelling *in vivo* evidence that CRP contributes to tissue damage in general.

The present application provides evidence concerning the conditions that are associated with tissue damage that involves elevated levels of CRP, thereby permitting one of skill in the art to identify type of tissue damage that can be prevented or treated in accordance with the present invention. As described in the present application "CRP is the classical acute phase protein, the circulating concentration of which increases dramatically in response to most forms of inflammation, tissue injury and infection, and the value (*i.e.*, the amount of

CRP) attained in most conditions correlates closely with the extent and activity of disease." *See* page 1, lines 11-15, citing an article by the present inventor in the Oxford Textbook of Medicine (3rd Ed., Vol. 2, 1996; identified as reference FR in the IDS filed July 9, 2001). This article teaches that a number of inflammatory and/or tissue damaging and conditions are associated with increased CRP production and major elevation of serum CRP concentration, including infections, allergic complications of infections, inflammatory disease, allograft rejection, malignant neoplasia, necrosis and trauma (*see* page 1528 and Table 2 on page